REMARKS

This paper is submitted in response to the October 17, 2005 Office Action for the above-identified patent application. Claims 42, 43, 48, 53, 55, 56, 82, 85-89, and 91-101 are pending. Claims 42-51, 53, 55, 56, 82, 85, 86, and 88-92 stand rejected. Claims 43-47, 49-51, 53, 55-56, 88-92 stand objected to. Claim 87 has been allowed. Claims 1-41, 44-47, 49-52, 54, 57-81, 83-84, and 90 have been canceled. Claims 42, 43, 48, 53, 55, 56, 85, 86, 89, 91 and 92 have been amended. Claims 93-101 have been newly added. The Amendments to the claims, and the newly added claims, are supported by the specification and the original listing of claims, and do not constitute new matter.

Applicants thank the Examiner for withdrawing the previous objections and rejections under 35 U.S.C. §112, 2nd paragraph.

Amendments to the Claims

Applicants have amended claim 42, 48, and 53 to delete reference to an "amino acid sequence comprising at least one immunogenic epitope." Applicants have also amended claims 42 and 53 to recite "... comprising the amino acid..."

Applicants have amended claims 43, 55, 56, 85, 86, 89, 91 and 92, to delete the term "said" in favor of the term "the" to place claims in proper phraseology.

Applicants have amended claims 43 and 55 to delete the dependency from claim 87. As amended, claims 43 and 55 depends solely from claim 42.

Claims 1-41, 52, 54, 57-81 and 83-84 were canceled previously. Applicants have canceled herein claims 44-47, 49-51 and 90 solely to overcome an objection that the claims depended on later-added claims. Applicants have added new claims 93-101, which correspond to canceled claims 44-47, 49-51 and 90, to correct the dependency of the pending claims. The newly added claims depend from earlier presented claims, and present no new subject matter. Applicants respectfully request entry of the amendments, which introduce no new matter.

The Objections Should be Withdrawn

The Examiner has objected to claims 43-47, 49-51, and 55-56 for depending directly or indirectly from later appearing claims. Applicants have added new claims 93-100 to place the claims in proper dependent form, so that claims only depend from earlier appearing claims.

The Examiner has objected to claim 43 as failing to further limit the subject matter of a previous claim, claim 87. Claim 43 has been amended to depend only from claim 42.

The Examiner has objected to claims 55 and 56, alleging that claims 55 and 56 broaden the scope of claim 87, from which claims 55 and 56 depend. Applicants have amended claims 55 and 56 to depend only from claim 42.

The Examiner has objected to the term "mammalian cell" in claims 48, 49, 53, 88, 89, and 90-92, contending that the specification defines only mammalian cell lines in a method of preparing a polypeptide. Applicants disagree. A mammalian cell line is a collection of cultured mammalian cells. The specification describes transfecting these cells with a synthetic nucleic acid (page 7, lines 30-32), and culturing the cells expressing the nucleic acid. A single cell is a necessary component of a mammalian cell line; there could not be a cell line without a single cell. Therefore, there is no basis for the objection.

In view of the amendments to the pending claims described above, Applicants request that the objections to the claims be withdrawn.

The Rejections

The Rejections Under 35 U.S.C. §101 Should Be Withdrawn

The Examiner alleges that claims 48-49, 53, 82, and 88-92 are directed to non-statutory subject matter for reciting the term "mammalian cell," which reads on cells present in a transfected mammal, which would include transfected humans. Applicants traverse.

The presently amended claims recite a method of preparing a polypeptide comprising transfecting a host cell with a nucleic acid encoding the polypeptide, culturing the transfected host cell under conditions where the nucleic acid is expressed, and recovering a polypeptide from the host cell. The claimed method requires a culturing step. Culturing a human cell as a tissue or an isolated cell, falls within the statutory subject matter. As such, Applicants request that the rejection be withdrawn.

The Rejections Under 35 U.S.C. §102(b) Should Be Withdrawn

Kuruazono Does Not Anticipate the Claimed Subject Matter

The Examiner has maintained the rejection of claims 42-47, 55 and 82 under 35 U.S.C. §102(b) as allegedly being anticipated by Kurazono *et al.* ("Minimal essential domains specifying toxicity of the light chains of tetanus toxin and botulinum neurotoxin type A" *J. Biol. Chem.*, 267, 14721-14729) (hereinafter "Kurazono") as evidenced by Dertzbaugh *et al.* ("Mapping of protective and cross-reactive domains of the type A neurotoxin of Clostridium botulinum," *Vaccine*, 14, 1538, 1996) (hereinafter "Dertzbaugh") and Binz *et al.* Swiss Prot Accession No. P10845 (hereinafter "Binz"). The Examiner alleges that Kurazono teaches (1) a nucleic acid that encodes at least one epitope held in common with SEQ ID NO 4; (2) an isolated or purified nucleic acid fragment of botulinum neurotoxin serotype A; (3) an amino acid sequence comprising at least one epitope of SEQ ID NO:4; (4) an expression vector comprising a nucleic acid encoding at least one epitope of SEQ ID NO:4.; (5) a nucleic acid wherein the AT content is less than about 70% of the total

base composition; and (6) a recombinant host cell comprising a nucleic acid of claim 45. Applicants respectfully traverse this rejection.

To support a rejection under 35 U.S.C. § 102(b), each and every feature of the rejected claim must be disclosed in a single prior art reference. Contrary to the suggestions of the Examiner, Kurazono does not disclose several limitations of the claimed invention. For example, Kurazono does not disclose or suggest, as claimed in claim 42 "a polypeptide comprising the amino acid sequence of SEQ ID NO:4." As presented in the response filed August 1, 2005 to the office action mailed March 31, 2005, Kurazono used mailed Binz's nucleic acid sequence (identified both as Genbank Accession No. M30196 and GI 144864), which encodes the amino acid sequence of Swiss Prot Accession No. P10845, which is the amino acid sequence of a wild-type botulinum neurotoxin serotype A heavy chain. Applicants reiterate that the amino acid sequence of SEQ ID NO:4 of the instant invention is not identical to the amino acid sequence of P10845. Applicants invite the Examiner's attention to a sequence alignment of the two sequences, submitted August 1, 2005 in response to the office action mailed March 31, 2005, and again herewith at Exhibit A. Applicant's SEQ ID NO:4 ("SEQ") differs from P1085 at position 1 (SEQ) and position 863 (P10845).

Moreover, with respect to claim 43, Applicants submit that Binz's nucleic acid sequence M30196/144864 is not identical to the nucleic acid sequence of SEQ ID NO:3 of the instant invention. Applicants invite the Examiner's attention to a sequence alignment of M30196/144864 and SEQ ID NO:3, submitted August 1, 2005 in response to the office action mailed March 31, 2005, and again herewith at Exhibit B. In the sequence alignment, "Sequence 1," ("Query") is nucleic acid sequence 144864; "Sequence 2," ("Sbjct") is SEQ ID NO:3. In the alignment, identical nucleotides are indicated by a bar between the aligned sequences. It is clearly evident that the sequence of Binz and that of SEQ ID NO:3 are not identical. Indeed, the "identity" score calculated by the alignment algorithm indicates that the two sequences are only 71% identical.

Furthermore, Applicants respectfully submit that the Examiner is using an improper interpretation of the claim language. The presently amended claims recite a polypeptide comprising the amino acid sequence of SEQ ID NO:4, a nucleic acid

comprising nucleotides 13-1314 of SEQ ID NO:3, and a nucleic acid comprising the nucleic acid sequence of SEQ ID NO:3. Applicants submit that the claims do not read upon fragments of these sequences, as the Examiner contends in the rejection. The transitional word "comprising" in the rejected claims does *not* encompass smaller entities. M.P.E.P. 2111.03 states that:

> The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., *Mars Inc. v. H.J. Heinz Co.*, 377 F.3d 1369, 1376, 71 USPQ2d 1837, 1843 (Fed. Cir. 2004) ("like the term 'comprising,' the terms 'containing' and 'mixture' are open-ended."); *Invitrogen Corp. v. Biocrest Mfg.*, L.P., 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 2003) ("The transition 'comprising' in a method claim indicates that the claim is open-ended and allows for additional steps."); *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) ("Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.).

Thus, at least for these reasons, applicants submit that Kurazono does not anticipate the claimed invention.

Nonetheless, Applicants have amended the claims to delete reference to an amino acid sequence "comprising at least one immunogenic epitope." The amended claims now recite "an isolated or purified nucleic acid sequence encoding a polypeptide having the amino acid sequence of SEQ ID NO: 4." Because the amino acid sequence of Kurazono differs from SEQ ID NO: 4 at position 863 (P10845) and position 1 (SEQ), Kurazono does not describe a nucleic acid sequence encoding SEQ ID NO: 4. Thus, in view of the amendments to the claims and because Kurazono does not teach or suggest the claimed subject matter, Applicants respectfully request that the rejection of claims 42-44, 45-47 and 82 under 35 U.S.C. §102(b) be withdrawn.

LaPenotiere and Thompson Do Not Anticipate the Claimed Subject Matter

The Examiner has maintained the rejection of claims 42-50, 53, 82, and 88-92 under 35 U.S.C. §102(b) as allegedly being anticipated by LaPenotiere *et al.* ("Development of molecular engineered vaccine for *C. Botulinum* neurotoxins," in

Botulinum and Tetanus Neurotoxins, Plenum Press, NY, 1993) (hereinafter "LaPenotiere") as evidenced by the New England Biolabs product description of pMal (see LaPenotiere page 464, paragraph 2, line 2), Atassi *et al.* ("Structure, activity, and immune (T and B cell)" in *Crit. Rev. Immunology*, 19, 219-260) (hereinafter "Atassi") and Clayton *et al.* ("Protective vaccination with a recombinant fragment of *Clostridium botulinum* neurotoxin serotype A expressed from a synthetic gene in *Escherichia coli*" in *Infect. Immunity*, 63, 2738-2742) (hereinafter "Clayton"). The Examiner alleges that LaPenotiere discloses a (1) a nucleic acid that encodes at least one epitope held in common with SEQ ID NO 4; (2) nucleic acid of botulinum neurotoxin serotype A Hc fragment, which, when expressed, induces a protective immune response; (3) an expression vector comprising the nucleic acid; (4) a host cell comprising the expression vector, and (5) a method of preparing a polypeptide comprising transfecting a cell with a nucleic acid having at least one immunogenic epitope of SEQ ID NO:4, culturing the transfected cells wherein the nucleic acid is expressed and recovering the insoluble polypeptide.

The Examiner has also maintained the rejection of claims 42-45, 28, 50, 55 and 80 as allegedly anticipated by Thompson *et al.* ("The complete amino acid sequence of the *Clostridium botulinum* type A neurotoxin, deduced by nucleotide analysis of the encoding gene," *Eur. J. Biochem*, 7, 1043, 1990) (hereinafter "Thompson"). The Examiner alleges that Thompson discloses (1) an isolated and purified nucleic acid comprising at least one immunogenic epitope encoded by SEQ ID NO:4 and a nucleic acid sequence of SEQ ID NO:3; (2) an expression vector comprising the nucleic acid; (3) a nucleic acid comprising less than about 70% d(A/T) content; (3) a recombinant host comprising the nucleic acid sequence; and (4) methods of preparing a polypeptide, comprising transfecting a cell with a nucleic acid encoding a polypeptide comprising an amino acid sequence that has at least one epitope of SEQ ID NO:4, and culturing the cell under conditions wherein the nucleic acid is expressed. Applicants respectfully traverse these rejections.

A stated in the response filed August 1, 2005 in response to the office action mailed March 31, 2005, both LaPenotiere and Thompson teach a nucleic acid sequence of a wild-type botulinum neurotoxin serotype A heavy chain. Moreover, both LaPenotiere and

Thompson utilized the same nucleic acid sequence that encodes a wild-type portion of the carboxy terminus of a botulinum neurotoxin type A heavy chain. In fact, LaPenotiere teaches that the nucleic acid sequence used therein was isolated from plasmid pCDA3 ("The DNA clone coding for the H_c domain of *C. botulinum* toxin serotype A was pCBA3, kindly provided by Nigel Minton."). *See* LaPenotiere, page 464, lines 15-16 (citing Thompson *et al.*, *Eur. J. Biochem.*, 189, 73, 1990). Thompson's nucleic acid sequence, identified as both Genbank Accession No. X52066 and GI 40381, encodes an amino acid sequence that is also identified as P10845. *See* Exhibit C, submitted August 1, 2005 in response to the office action issued March 31, 2005, and again herewith, at page 3, highlighted in yellow. As shown by the alignment at Exhibit A, the amino acid sequence of SEQ ID NO:4 and the amino acid sequence of P10845 are not the same.

Moreover, as discussed above, the nucleic acid sequence of SEQ ID NO:3 as instantly claimed, is not identical to the nucleic acid sequence of X50266. Applicants invite the Examiner's attention to a sequence alignment of the two sequences, attached hereto at Exhibit D, which was originally submitted August 1, 2005 in response to the office action mailed March 31, 2005. In the sequence alignment, Sequence 1 ("Query") is Thompson's nucleic acid sequence, GI 40381; Sequence 2 ("Sbjct") is SEQ ID NO:3 of the instant invention. As shown in the alignment, identical nucleotides are indicated by a bar between the aligned sequences. As pointed out above, the two sequences are simply not identical, as evidenced by this alignment. Applicants respectfully remind the Examiner that the claims do not read on fragments of the sequences, and therefore, submit that, for at least these reasons, neither LaPenotiere nor Thompson anticipate the instant claims.

Nonetheless, Applicants have amended the claims to delete reference to an amino acid sequence "comprising at least one immunogenic epitope." The amended claims now recite "an isolated or purified nucleic acid sequence encoding a polypeptide having the amino acid sequence of SEQ ID NO: 4." Because the amino acid sequence of LaPenotiere and Thompson differ from SEQ ID NO: 4 at position 863 (P10845) and position 1 (SEQ), LaPenotiere and Thompson do not describe a nucleic acid sequence encoding SEQ ID NO: 4.

Thus, in view of the above arguments and the amendments to the claims, LaPenotiere and Thompson do not disclose the subject matter of the claims as amended. Applicants respectfully request that the rejection of claims 42-50, 53, 82 and 88-92 as anticipated by LaPenotiere, and claims 42-45, 48, 50 and 82 as anticipated by Thompson, under 35 U.S.C. §102(b), be withdrawn.

Romanos Does Not Anticipate the Claimed Subject Matter

The Examiner has rejected claims 42, 48-49, 51, 53, 55, 56, 85-86, and 88-92 under 35 U.S.C. §102(b) as allegedly being anticipated by Romanos *et al.* ("Expression of tetanus toxin fragment C in yeast: gene synthesis is required to eliminate fortuitous polyadenylation sites in AT-rich DNA," in *Nucleic Acids Res.*, 19, 1461-1467) (hereinafter "Romanos") as evidenced by Atassi. The Examiner alleges that Romanos discloses a nucleic acid that encodes at least one epitope of SEQ ID NO: 4. Romanos discloses a fragment-C domain of tetanus toxin that shares conserved amino acids with botulinum toxin typeA, as shown by Atassi in Figure 14 and Table 5 at pages 248 and 249. Furthermore, the Examiner contends that the nucleic acid of Romanos comprises an overall AT content of about 63%, and is expressed to levels of over 25% of the total cell protein in a recombinant host cell which includes *Pichia pastoris*. Applicants respectfully traverse this rejection.

As described above, Applicants have amended the claims to delete reference to an amino acid sequence "comprising at least one immunogenic epitope." The amended claims now recite "an isolated or purified nucleic acid sequence encoding a polypeptide having the amino acid sequence of SEQ ID NO: 4." Atassi shows that the tetanus toxin amino acid sequence encoded by the nucleic acid of Romanos shares conserved epitopes with the wild-type heavy chain fragment-C domain of the botulinum neurotoxin serotype A (Swiss Prot Accession No. P10845). The tetanus toxin amino acid sequence of Romanos and Atassi is defined by Genbank Accession No. P04958 (submitted herewith as Exhibit E). Applicants invite the Examiner's attention to a sequence alignment of SEQ ID NO: 4 ("SEQ") and the amino acid sequence of tetanus toxin P04958 ("TETX_CLOTE") submitted herewith as Exhibit F. Applicants' SEQ ID NO:4 ("SEQ") differs from P04958 at numerous positions throughout the two sequences. The claimed invention is drawn to a

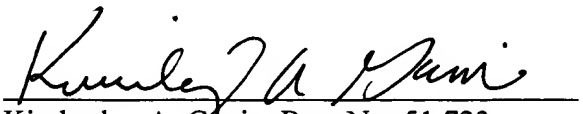
nucleic acid encoding SEQ ID NO:4, and therefore clearly differs from the amino acid sequence of Romanos. Applicants again respectfully remind the Examiner that the claims do not read on fragments of the sequences, and therefore Romanos does not disclose a nucleic acid encoding an amino acid sequence of SEQ ID NO: 4, and thus does not disclose every feature of the instant claims. Applicants respectfully request that the rejection of claims 42, 48-49, 51, 53, 55, 56, 85-86, and 88-92 under 35 U.S.C. §102(b) be withdrawn.

Conclusion

Applicants believe that the application is in condition for allowance and respectfully request favorable action. The Examiner is kindly invited to contact the undersigned if helpful to advance the application to allowance. An early allowance is earnestly sought.

In addition to the fees disclosed above for the petition for an extension of time to file this Response and a Request for Continued Examination, Applicants believe that no additional fees are due. In the event that fees are due, or overpayment is made, however, the Director is hereby authorized to charge payment of any such fees, or to credit any overpayment, to Deposit Account No. 02-4377.

Respectfully submitted,



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